Connecting via Winsock to STN

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LOGINID:SSPTAMXG1614

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	FEB 28	PATDPAFULL - New display fields provide for legal status data from INPADOC
NEWS	4	FEB 28	BABS - Current-awareness alerts (SDIs) available
NEWS	5	MAR 02	GBFULL: New full-text patent database on STN
NEWS	6	MAR 03	REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS	7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS	8	MAR 22	KOREAPAT now updated monthly; patent information enhanced
NEWS	9	MAR 22	Original IDE display format returns to REGISTRY/ZREGISTRY
NEWS	10	MAR 22	PATDPASPC - New patent database available
NEWS	11	MAR 22	REGISTRY/ZREGISTRY enhanced with experimental property tags
NEWS	12	APR 04	EPFULL enhanced with additional patent information and new fields
NEWS	13	APR 04	EMBASE - Database reloaded and enhanced
NEWS	14	APR 18	New CAS Information Use Policies available online
NEWS	15	APR 25	Patent searching, including current-awareness alerts (SDIs), based on application date in CA/CAplus and USPATFULL/USPAT2 may be affected by a change in filing date for U.S. applications.
NEWS	16	APR 28	Improved searching of U.S. Patent Classifications for U.S. patent records in CA/CAplus
NEWS	17	MAY 23	GBFULL enhanced with patent drawing images
NEWS	18	MAY 23	REGISTRY has been enhanced with source information from CHEMCATS
NEWS	19	JUN 06	The Analysis Edition of STN Express with Discover! (Version 8.0 for Windows) now available
NEWS	20	JUN 13	RUSSIAPAT: New full-text patent database on STN
NEWS	21	JUN 13	FRFULL enhanced with patent drawing images
NEWS	22	JUN 27	MARPAT displays enhanced with expanded G-group definitions and text labels
NEWS	23	JUL 01	MEDICONF removed from STN
NEWS	24	JUL 07	STN Patent Forums to be held in July 2005
NEWS	25	JUL 13	SCISEARCH reloaded
NEWS	26	JUL 20	Powerful new interactive analysis and visualization software, STN AnaVist, now available
NEWS	27	AUG 11	Derwent World Patents Index(R) web-based training during August
NEWS	28	AUG 11	STN AnaVist workshops to be held in North America

NEWS EXPRESS JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:19:44 ON 22 AUG 2005

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 13:19:54 ON 22 AUG 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 19 AUG 2005 HIGHEST RN 861198-35-8
DICTIONARY FILE UPDATES: 19 AUG 2005 HIGHEST RN 861198-35-8

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

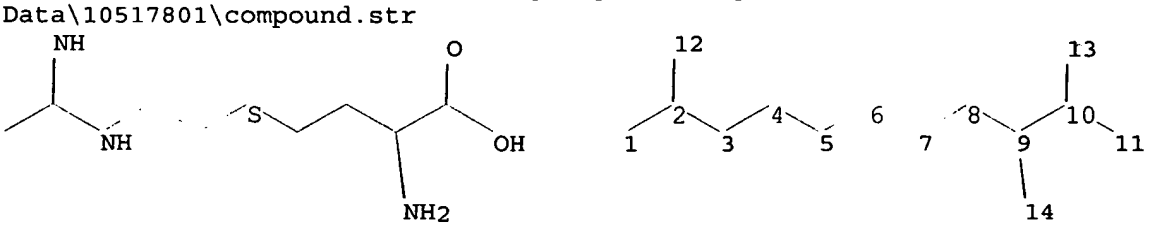
Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\Documents and Settings\mgraffeo\My Documents\Critical Data\10517801\compound.str



```
chain nodes :
1  2  3  4  5  6  7  8  9  10  11  12  13  14
chain bonds :
1-2  2-3  2-12  3-4  4-5  5-6  6-7  7-8  8-9  9-10  9-14  10-11  10-13
exact/norm bonds :
2-3  2-12  3-4  5-6  6-7  9-14
exact bonds :
1-2  4-5  7-8  8-9  9-10
normalized bonds :
10-11  10-13


Match level :
1:CLASS  2:CLASS  3:CLASS  4:CLASS  5:CLASS  6:CLASS  7:CLASS  8:CLASS  9:CLASS
10:CLASS  11:CLASS  12:CLASS  13:CLASS  14:CLASS

Stereo Bonds:

14-9 (Single Hash).


Stereo Chiral Centers:

9    (Parity=Don't Care)

Stereo RSS Sets:

Type=Relative (Default). 1 Nodes= 9

L1      STRUCTURE UPLOADED

=>  s l1 sss full
FULL SEARCH INITIATED 13:20:10 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    131 TO ITERATE

100.0% PROCESSED      131 ITERATIONS                              16 ANSWERS
SEARCH TIME: 00.00.01

L2           16 SEA SSS FUL L1

=> s l1 exa full
FULL SEARCH INITIATED 13:20:20 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      8 TO ITERATE

100.0% PROCESSED        8 ITERATIONS                               2 ANSWERS
SEARCH TIME: 00.00.01

L3            2 SEA EXA FUL L1

=> file caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               215.58     215.79

FILE 'CAPLUS' ENTERED AT 13:20:28 ON 22 AUG 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)


Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
```

FILE COVERS 1907 - 22 Aug 2005 VOL 143 ISS 9
FILE LAST UPDATED: 21 Aug 2005 (20050821/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s l2 or l3
            16 L2
            13 L3
L4          16 L2 OR L3

=> s l4 (L) antioxidant
         99349 ANTIOXIDANT
L5           0 L4 (L) ANTIOXIDANT

=> s l4 and chelat?
        126712 CHELAT?
L6           1 L4 AND CHELAT?

=> d bib abs hitstr
```

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:2680 CAPLUS
DN 140:65201
TI (2S)-2-Amino-4-{[2-(ethanimidoylamino)ethyl]thio}butanoic acid nitric oxide synthase inhibitor in stabilized pharmaceutical dosage forms
IN Broughton, Stuart James; Gharu, Rajinder Kumar; Leow, Mark Yuon Tuck; Neale, Philip John
PA SB Pharmco Puerto Rico Inc., P. R.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

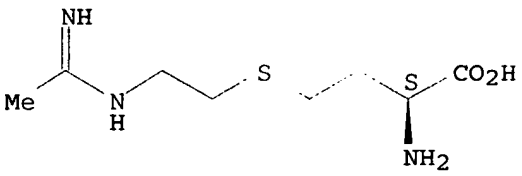
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004000296	A1	20031231	WO 2003-EP6465	20030619
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1513511	A1	20050316	EP 2003-740281	20030619
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI	GB 2002-14147	A	20020619		
	WO 2003-EP6465	W	20030619		

AB Pharmaceutical compns. comprising (2S)-MeC(:NH)NHCH2CH2SCH2CH2CH(NH2)CO2H (I) a pharmaceutically acceptable bulking agent and one or more antioxidants or **chelating** agents are described. A direct compression formula for tablets contained I, EDTA, Avical PH101, silica, and Mg stearate.

IT **210354-22-6 438542-15-5 638198-40-0**
638198-41-1
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
((2S)-2-Amino-4-{[2-(ethanimidoylamino)ethyl]thio}butanoic acid nitric oxide synthase inhibitor in stabilized pharmaceutical dosage forms)

RN 210354-22-6 CAPLUS
CN L-Homocysteine, S-[2-[(1-iminoethyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

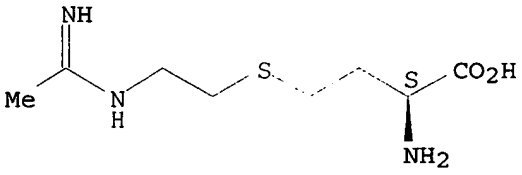


RN 438542-15-5 CAPLUS
CN L-Homocysteine, S-[2-[(1-iminoethyl)amino]ethyl]-, phosphate (1:1) (9CI) (CA INDEX NAME)

CM 1

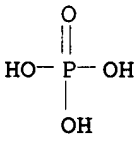
CRN 210354-22-6
CMF C8 H17 N3 O2 S

Absolute stereochemistry.



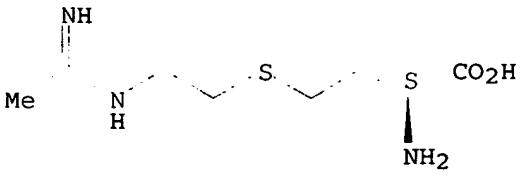
CM 2

CRN 7664-38-2
CMF H3 O4 P



RN 638198-40-0 CAPLUS
CN L-Homocysteine, S-[2-[(1-iminoethyl)amino]ethyl]-, monohydrate (9CI) (CA INDEX NAME)

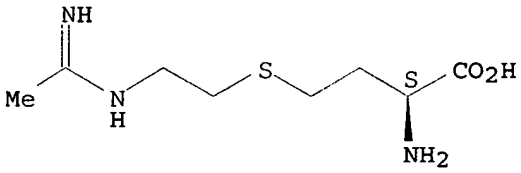
Absolute stereochemistry.



● H_2O

RN 638198-41-1 CAPLUS
CN L-Homocysteine, S-[2-[(1-iminoethyl)amino]ethyl]-, trihydrate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●3 H_2O

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> s l4 (L) (edta or "ethylenediamintetraacetic acid" or malic or ascorbic)
         82261 EDTA
            12 "ETHYLENEDIAMINTETRAACETIC"
       4020182 "ACID"
            11 "ETHYLENEDIAMINTETRAACETIC ACID"
                 ("ETHYLENEDIAMINTETRAACETIC"(W)"ACID")
         29892 MALIC
         78739 ASCORBIC
L7            0 L4 (L) (EDTA OR "ETHYLENEDIAMINTETRAACETIC ACID" OR MALIC OR
                ASCORBIC)

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              20.42     236.21

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
```

```
                                                          ENTRY    SESSION
CA SUBSCRIBER PRICE                                       -0.73      -0.73

STN INTERNATIONAL LOGOFF AT 13:23:20 ON 22 AUG 2005


Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:SSPTAMXG1614

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  FEB 28   PATDPAFULL - New display fields provide for legal status
                   data from INPADOC
 NEWS  4  FEB 28   BABS - Current-awareness alerts (SDIs) available
 NEWS  5  MAR 02   GBFULL: New full-text patent database on STN
 NEWS  6  MAR 03   REGISTRY/ZREGISTRY - Sequence annotations enhanced
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 NEWS  10 MAR 22   PATDPASPC - New patent database available
 NEWS  11 MAR 22   REGISTRY/ZREGISTRY enhanced with experimental property tags
 NEWS  12 APR 04   EPFULL enhanced with additional patent information and new
                   fields
 NEWS  13 APR 04   EMBASE - Database reloaded and enhanced
 NEWS  14 APR 18   New CAS Information Use Policies available online
 NEWS  15 APR 25   Patent searching, including current-awareness alerts (SDIs),
                   based on application date in CA/CAplus and USPATFULL/USPAT2
                   may be affected by a change in filing date for U.S.
                   applications.
 NEWS  16 APR 28   Improved searching of U.S. Patent Classifications for
                   U.S. patent records in CA/CAplus
 NEWS  17 MAY 23   GBFULL enhanced with patent drawing images
 NEWS  18 MAY 23   REGISTRY has been enhanced with source information from
                   CHEMCATS
 NEWS  19 JUN 06   The Analysis Edition of STN Express with Discover!
                   (Version 8.0 for Windows) now available
 NEWS  20 JUN 13   RUSSIAPAT: New full-text patent database on STN
 NEWS  21 JUN 13   FRFULL enhanced with patent drawing images
 NEWS  22 JUN 27   MARPAT displays enhanced with expanded G-group definitions
                   and text labels
 NEWS  23 JUL 01   MEDICONF removed from STN
 NEWS  24 JUL 07   STN Patent Forums to be held in July 2005
 NEWS  25 JUL 13   SCISEARCH reloaded
 NEWS  26 JUL 20   Powerful new interactive analysis and visualization software,
                   STN AnaVist, now available
 NEWS  27 AUG 11   Derwent World Patents Index(R) web-based training during
                   August
 NEWS  28 AUG 11   STN AnaVist workshops to be held in North America

 NEWS EXPRESS  JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005
```

```
 NEWS HOURS     STN Operating Hours Plus Help Desk Availability
 NEWS INTER     General Internet Information
 NEWS LOGIN     Welcome Banner and News Items
 NEWS PHONE     Direct Dial and Telecommunication Network Access to STN
 NEWS WWW       CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

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  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:57:13 ON 22 AUG 2005

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

FILE 'REGISTRY' ENTERED AT 14:57:25 ON 22 AUG 2005
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   19 AUG 2005  HIGHEST RN 861198-35-8
DICTIONARY FILE UPDATES:  19 AUG 2005  HIGHEST RN 861198-35-8

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

*********************************************************************
*                                                                   *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                   *
*********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\Documents and Settings\mgraffeo\My Documents\Critical
Data\10517801\compound.str
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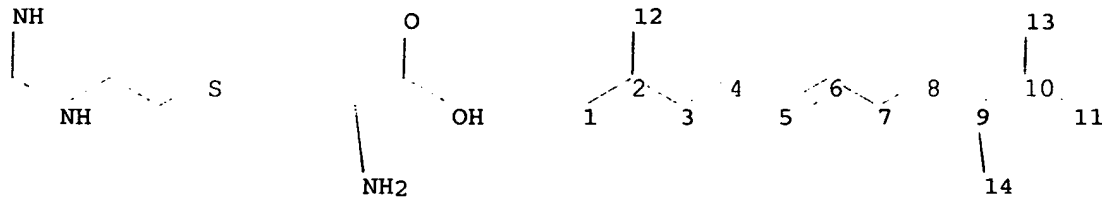


chain nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14
chain bonds :
1-2 2-3 2-12 3-4 4-5 5-6 6-7 7-8 8-9 9-10 9-14 10-11 10-13
exact/norm bonds :
2-3 2-12 3-4 5-6 6-7 9-14
exact bonds :
1-2 4-5 7-8 8-9 9-10
normalized bonds :
10-11 10-13

Match level :
1:CLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS
10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS

Stereo Bonds:

14-9 (Single Hash).

Stereo Chiral Centers:

9 (Parity=Don't Care)

Stereo RSS Sets:

Type=Relative (Default). 1 Nodes= 9

L1 STRUCTURE UPLOADED

=> s l1 exa full
FULL SEARCH INITIATED 14:57:50 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 8 TO ITERATE

100.0% PROCESSED 8 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

L2 2 SEA EXA FUL L1

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	54.68	54.89

FILE 'CAPLUS' ENTERED AT 14:57:58 ON 22 AUG 2005

FILE COVERS 1907 - 22 Aug 2005 VOL 143 ISS 9
FILE LAST UPDATED: 21 Aug 2005 (20050821/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s l2 and (malic or edta or edetic or ascorbic)
            13 L2
         29892 MALIC
         82261 EDTA
           227 EDETIC
         78739 ASCORBIC
L3           1 L2 AND (MALIC OR EDTA OR EDETIC OR ASCORBIC)

=> d bib abs hitstr
```

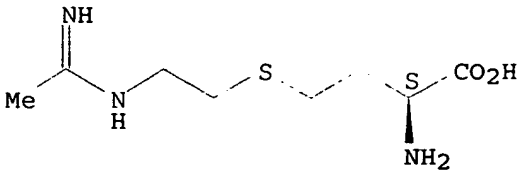
L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:2680 CAPLUS
DN 140:65201
TI (2S)-2-Amino-4-{[2-(ethanimidoylamino)ethyl]thio}butanoic acid nitric oxide synthase inhibitor in stabilized pharmaceutical dosage forms
IN Broughton, Stuart James; Gharu, Rajinder Kumar; Leow, Mark Yuon Tuck; Neale, Philip John
PA SB Pharmco Puerto Rico Inc., P. R.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004000296	A1	20031231	WO 2003-EP6465	20030619
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1513511	A1	20050316	EP 2003-740281	20030619
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI	GB 2002-14147	A	20020619		
	WO 2003-EP6465	W	20030619		

AB Pharmaceutical compns. comprising (2S)-MeC(:NH)NHCH2CH2SCH2CH2CH(NH2)CO2H (I) a pharmaceutically acceptable bulking agent and one or more antioxidants or chelating agents are described. A direct compression formula for tablets contained I, **EDTA**, Avical PH101, silica, and Mg stearate.
IT **210354-22-6**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
((2S)-2-Amino-4-{[2-(ethanimidoylamino)ethyl]thio}butanoic acid nitric oxide synthase inhibitor in stabilized pharmaceutical dosage forms)
RN 210354-22-6 CAPLUS

CN L-Homocysteine, S-[2-[(1-iminoethyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> s l2 and stability
           13 L2
       623742 STABILITY
L4          0 L2 AND STABILITY

=> s l2 and formulation
           13 L2
       126374 FORMULATION
L5          0 L2 AND FORMULATION

=> s l2 (antioxidant or chelat?)
MISSING OPERATOR 'L2 (ANTIOXIDAN'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l2 and (antioxidant or chelat?)
           13 L2
        99349 ANTIOXIDANT
       126712 CHELAT?
L6          1 L2 AND (ANTIOXIDANT OR CHELAT?)

=> d bib abs

L6   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   2004:2680  CAPLUS
DN   140:65201
TI   (2S)-2-Amino-4-{[2-(ethanimidoylamino)ethyl]thio}butanoic acid nitric
     oxide synthase inhibitor in stabilized pharmaceutical dosage forms
IN   Broughton, Stuart James; Gharu, Rajinder Kumar; Leow, Mark Yuon Tuck;
     Neale, Philip John
PA   SB Pharmco Puerto Rico Inc., P. R.
SO   PCT Int. Appl., 16 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   WO 2004000296        A1    20031231    WO 2003-EP6465         20030619
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR,
             TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
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EP 1513511 A1 20050316 EP 2003-740281 20030619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
PRAI GB 2002-14147 A 20020619
WO 2003-EP6465 W 20030619
AB Pharmaceutical compns. comprising (2S)-MeC(:NH)NHCH2CH2SCH2CH2CH(NH2)CO2H (I) a pharmaceutically acceptable bulking agent and one or more antioxidants or **chelating** agents are described. A direct compression formula for tablets contained I, EDTA, Avical PH101, silica, and Mg stearate.
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l2
L7 13 L2

=> d 1-13 bib abs

L7 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:465475 CAPLUS
DN 143:71325
TI GW274150 and GW273629 are potent and highly selective inhibitors of inducible nitric oxide synthase in vitro and in vivo
AU Alderton, Wendy K.; Angell, Anthony D. R.; Craig, Caroline; Dawson, John; Garvey, Edward; Moncada, Salvador; Monkhouse, Jayne; Rees, Daryl; Russell, Linda J.; Russell, Rachel J.; Schwartz, Sheila; Waslidge, Neil; Knowles, Richard G.
CS Medicines Research Centre, Respiratory & Inflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline Research, Stevenage, SG1 2NY, UK
SO British Journal of Pharmacology (2005), 145(3), 301-312
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
AB GW274150 ([2-[(1-iminoethyl) amino]ethyl]-L-homocysteine) and GW273629 (3-[[2-[(1-iminoethyl)amino]ethyl]sulfonyl]-L-alanine) are potent, time-dependent, highly selective inhibitors of human inducible nitric oxide synthase (iNOS) vs. endothelial NOS (eNOS) (>100-fold) or neuronal NOS (nNOS) (>80-fold). GW274150 and GW273629 are arginine competitive, NADPH-dependent inhibitors of human iNOS with steady state Kd values of <40 and <90 nM, resp. GW274150 and GW273629 inhibited intracellular iNOS in J774 cells in a time-dependent manner, reaching IC50 values of 0.2±0.04 and 1.3±0.16 μM, resp. They were also acutely selective in intact rat tissues: GW274150 was >260-fold and 219-fold selective for iNOS against eNOS and nNOS, resp., while GW273629 was >150-fold and 365-fold selective for iNOS against eNOS and nNOS, resp. The pharmacokinetic profile of GW274150 was biphasic in healthy rats and mice with a terminal half-life of .apprx.6 h. That of GW273629 was also biphasic in rats, producing a terminal half-life of .apprx.3 h. In mice however, elimination of GW273629 appeared monophasic and more rapid (.apprx.10 min). Both compds. show a high oral bioavailability (>90%) in rats and mice. GW274150 was effective in inhibiting LPS-induced plasma NOx levels in mice with an ED50 of 3.2±0.7 mg kg-1 after 14 h i.p. and 3.8±1.5 mg kg-1 after 14 h when administered orally. GW274150 was effective in inhibiting LPS-induced plasma NOx levels in mice with an ED50 of 3.2±0.7 mg kg-1 after 14 h i.p. and 3.8±1.5 mg kg-1 after 14 h when administered orally. GW273629 showed shorter-lived effects on plasma NOx and an ED50 of 9±2 mg kg-1 after 2 h when administered i.p. The effects of GW274150 and GW273629 in vivo were consistent with high selectivity for iNOS, as these inhibitors were of low potency against nNOS in the rat cerebellum and did not cause significant effects on blood pressure in instrumented mice.
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:48432 CAPLUS
DN 142:169464
TI Beneficial effects of GW274150 treatment on the development of experimental colitis induced by dinitrobenzene sulfonic acid
AU Di Paola, Rosanna; Mazzon, Emanuela; Patel, Nimesh S. A.; Genovese, Tiziana; Muia, Carmelo; Thiemermann, Christoph; De Sarro, Angelina; Cuzzocrea, Salvatore
CS Department of Clinical and Experimental Medicine and Pharmacology, School of Medicine, Policlinico Universitario, University of Messina Torre Biologica, Messina, 98123, Italy
SO European Journal of Pharmacology (2005), 507(1-3), 281-289
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier B.V.
DT Journal
LA English
AB Inflammatory bowel disease is associated with inducible nitric oxide synthase (iNOS) expression, oxidative and nitrosative stress, and leukocyte infiltration in the colon. Here, the authors investigate the effects of the selective iNOS-inhibitor (S)-2-amino-(1-iminoethylamino)-5-thiopentanoic acid (GW274150) on the development of exptl. colitis induced by dinitrobenzene sulfonic acid. When compared to dinitrobenzene sulfonic acid-treated mice, GW274150 (5 mg/kg i.p.)-treated mice subjected to dinitrobenzene sulfonic ACID-induced colitis experienced a significantly lower rate of the extent and severity of the histol. signs of colon injury. Dinitrobenzene sulfonic acid-treated mice experienced hemorrhagic diarrhea and weight loss. At 4 days after the administration of dinitrobenzene sulfonic acid, the mucosa of the colon exhibited large areas of necrosis. Immunohistochem. for nitrotyrosine and poly (ADP-ribose) (PAR) showed an intense staining in the inflamed colon. Treatment of dinitrobenzene sulfonic acid-treated mice with GW274150 significantly reduced the degree of hemorrhagic diarrhea and weight loss caused by administration of dinitrobenzene sulfonic acid. GW274150 also caused a substantial reduction of (i) the degree of colon injury, (ii) the rise in myeloperoxidase (MPO) activity (mucosa), (iii) the increase in staining (immunohistochem.) for nitrotyrosine, as well as (iv) PARP activation caused by dinitrobenzene sulfonic acid in the colon. Thus, GW274150 treatment reduced the degree of colitis caused by dinitrobenzene sulfonic acid. The authors propose that selective inhibition of iNOS activity with GW274150 may be useful in the treatment of inflammatory bowel disease.
RE.CNT 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:346162 CAPLUS
DN 140:399632
TI Effects of GW274150, a novel and selective inhibitor of iNOS activity, in acute lung inflammation
AU Dugo, Laura; Marzocco, Stefania; Mazzon, Emanuela; Di Paola, Rosanna; Genovese, Tiziana; Caputi, Achille P.; Cuzzocrea, Salvatore
CS Department Clinical and Experimental Medicine and Pharmacology, University of Messina, Messina, 98100, Italy
SO British Journal of Pharmacology (2004), 141(6), 979-987
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
AB The aim of this study was to investigate the effect of GW274150, a novel, potent and selective inhibitor of inducible nitric oxide synthase (iNOS) activity in a model of lung injury induced by carrageenan administration in the rats. Injection of carrageenan into the pleural cavity of rats elicited an acute inflammatory response characterized by: fluid accumulation in the pleural cavity which contained a large number of

polymorphonuclear cells (PMNs) as well as an infiltration of PMNs in lung tissues and subsequent lipid peroxidn., and increased production of nitrite/nitrate (NOx), tumor necrosis factor α (TNF-α) and interleukin-1β (IL-1β). All parameters of inflammation were attenuated in a dose-dependent manner by GW274150 (2.5, 5 and 10 mg kg-1 injected i.p. 5 min before carrageenan). Carrageenan induced an upregulation of the intracellular adhesion mols.-1 (ICAM-1), as well as nitrotyrosine and poly (ADP-ribose) (PAR) as determined by immunohistochem. anal. of lung tissues. The degree of staining for the ICAM-1, nitrotyrosine and PAR was reduced by GW274150. These results clearly confirm that NO from iNOS plays a role in the development of the inflammatory response by altering key components of the inflammatory cascade. GW274150 may offer a novel therapeutic approach for the management of various inflammatory diseases where NO and related radicals have been postulated to play a role.

RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:2680 CAPLUS
DN 140:65201
TI (2S)-2-Amino-4-{[2-(ethanimidoylamino)ethyl]thio}butanoic acid nitric oxide synthase inhibitor in stabilized pharmaceutical dosage forms
IN Broughton, Stuart James; Gharu, Rajinder Kumar; Leow, Mark Yuon Tuck; Neale, Philip John
PA SB Pharmco Puerto Rico Inc., P. R.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004000296	A1	20031231	WO 2003-EP6465	20030619
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1513511	A1	20050316	EP 2003-740281	20030619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI GB 2002-14147	A	20020619		
WO 2003-EP6465	W	20030619		

AB Pharmaceutical compns. comprising (2S)-MeC(:NH)NHCH2CH2SCH2CH2CH(NH2)CO2H (I) a pharmaceutically acceptable bulking agent and one or more antioxidants or chelating agents are described. A direct compression formula for tablets contained I, EDTA, Avical PH101, silica, and Mg stearate.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:947089 CAPLUS
DN 140:314741
TI GW274150 inhibits nitric oxide production by primary cultures of rat proximal tubular cells
AU Chatterjee, Prabal K.; Kvale, Espen O.; Patel, Nimesh S. A.; Thiemermann, Christoph
CS Department of Experimental Medicine, Nephrology & Critical Care, William

Harvey Research Institute, Queen Mary - University of London, UK
SO Medical Science Monitor (2003), 9(10), BR357-BR362
CODEN: MSMOFR; ISSN: 1234-1010
PB International Scientific Literature, Inc.
DT Journal
LA English
AB Background: Production of nitric oxide (NO) subsequent to expression of inducible NO synthase (iNOS) contributes to the development of ischemic renal injury and inflammation. Here the authors investigate the effects of GW274150, a potent, long-acting and highly selective inhibitor of iNOS activity, on NO production by primary cultures of rat proximal tubular cells (PTC). Material/Methods: Pure populations of PTC were isolated from the cortex of kidneys obtained from male Wistar rats using a combination of collagenase digestion, sieving and Percoll centrifugation. Confluent PTC cultures were incubated for 1-24 h with MEM, interferon-γ (IFN-γ, 100 iu/mL), bacterial lipopolysaccharide (LPS, 10 μg/mL) in combination after which NO production was determined PTC were also incubated with IFN-γ (100 iu/mL) and LPS (10 μg/mL) and increasing concns. of GW274150 or L-N6-(1-iminoethyl)lysine (L-NIL) (10 nM - 1 mM) for 24 h after which nitrite levels in the incubation medium were measured. Results: IFN-γ and LPS in combination produced a significant, time-dependent increase in NO production Both GW274150 and L-NIL produced a significant and concentration-dependent inhibition of NO production However, GW274150 was markedly more potent (EC50 .apprx. 100 nM) than L-NIL (EC50 .apprx. 10 μM). Conclusions: GW274150 inhibits NO production by primary cultures of PTCs and may therefore be useful in conditions associated with nitrosative stress of the kidney.
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:300915 CAPLUS
DN 138:302642
TI Inducible nitric oxide synthase inhibitors as vaccine adjuvants
IN Thomsen, Lindy Louise
PA Glaxo Group Limited, UK
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003030935	A2	20030417	WO 2002-GB4365	20020926
	WO 2003030935	A3	20030814		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2462582	AA	20030417	CA 2002-2462582	20020926
	EP 1432440	A2	20040630	EP 2002-762572	20020926
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
	JP 2005510478	T2	20050421	JP 2003-533966	20020926
	US 2005054726	A1	20050310	US 2004-491843	20041011
PRAI	GB 2001-24022	A	20011005		
	WO 2002-GB4365	W	20020926		

OS MARPAT 138:302642

AB The present invention relates to the use of inducible nitric oxide synthase (iNOS) inhibitors as vaccine adjuvants, and in a preferred aspect of the invention they are used for adjuvanting nucleic acid (DNA) vaccines. The iNOS inhibitors preferably provide for an increase in antigen-specific CD4-pos. and/or CD8-pos. T cells. These compds. preferably induce a Th1-biased immune response as measured by increased formation of Th1 cytokines, in particular interferon γ. The present invention further provides pharmaceutical compns. comprising an antigen and the inhibitor.

L7 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:289025 CAPLUS
DN 139:301665
TI GW274150, a potent and highly selective inhibitor of iNOS, reduces experimental renal ischemia/reperfusion injury
AU Chatterjee, Prabal K.; Patel, Nimesh S. A.; Sivarajah, Ahila; Kvale, Espen O.; Dugo, Laura; Cuzzocrea, Salvatore; Brown, Paul A. J.; Stewart, Keith N.; Mota-Filipe, Helder; Britti, Domenico; Yaqoob, Muhammad M.; Thiemermann, Christoph
CS Department of Experimental Medicine and Nephrology, The William Harvey Research Institute, Queen Mary, University of London, London, UK
SO Kidney International (2003), 63(3), 853-865
CODEN: KDYIA5; ISSN: 0085-2538
PB Blackwell Publishing, Inc.
DT Journal
LA English
AB Generation of nitric oxide (NO) by inducible nitric oxide synthase (iNOS) may contribute to renal ischemia/reperfusion (I/R) injury. The aim of this study was to investigate the effects of GW274150, a novel, highly selective, potent and long-acting inhibitor of iNOS activity in rat and mouse models of renal I/R. Rats were administered GW274150 (5 mg/kg i.v. bolus administered 30 min prior to I/R) and subjected to bilateral renal ischemia (45 min) followed by reperfusion (6 h). Serum and urinary indicators of renal dysfunction, tubular and reperfusion injury were measured, specifically, serum urea, creatinine, aspartate aminotransferase (AST) and N-acetyl-β-D-glucosaminidase (NAG) enzymuria. In addition, renal sections were used for histol. scoring of renal injury and for immunol. evidence of nitrotyrosine formation and poly [ADP (ADP)-ribose] (PAR). Nitrate levels were measured in rat plasma using the Griess assay. Mice (wild-type, administered 5 mg/kg GW274150, and iNOS-/-) were subjected to bilateral renal ischemia (30 min) followed by reperfusion (24 h) after which renal dysfunction (serum urea, creatinine), renal myeloperoxidase (MPO) activity and malondialdehyde (MDA) levels were measured. GW274150, administered prior to I/R, significantly reduced serum urea, serum creatinine, AST, and NAG indicating reduction of renal dysfunction and injury caused by I/R. GW274150 reduced histol. evidence of tubular injury and markedly reduced immunohistochem. evidence of nitrotyrosine and PAR formation, indicating reduced peroxynitrite formation and poly (ADP-ribose) polymerase (PARP) activation, resp. GW274150 abolished the rise in the plasma levels of nitrate (indicating reduced NO production). GW274150 also reduced the renal dysfunction in wild-type mice to levels similar to that observed in iNOS-/- mice subjected to I/R. Renal MPO activity and MDA levels were significantly reduced in wild-type mice administered GW274150 and iNOS-/- mice subjected to renal I/R, indicating reduced polymorphonuclear leukocyte (PMN) infiltration and lipid peroxidn. These results suggest that (1) an enhanced formation of NO by iNOS contributes to the pathophysiol. of renal I/R injury and (2) GW274150 reduces I/R injury of the kidney. We propose that selective inhibitors of iNOS activity may be useful against renal dysfunction and injury associated with I/R of the kidney.
RE.CNT 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:51504 CAPLUS

DN 139:159864
TI A novel, potent and selective inhibitor of the activity of inducible nitric oxide synthase (GW274150) reduces the organ injury in hemorrhagic shock
AU McDonald, M. C.; Izumi, M.; Cuzzocrea, S.; Thiemermann, C.
CS The William Harvey Research Institute, St. Bartholomew's and The Royal London School of Medicine and Dentistry, London, EC1M6BQ, UK
SO Journal of Physiology and Pharmacology (2002), 53(4, Pt. 1), 555-569
CODEN: JPHPEI; ISSN: 0867-5910
PB Polish Physiological Society
DT Journal
LA English
AB An enhanced formation of nitric oxide (NO) by the inducible NO synthase (iNOS) may contribute to the pathophysiol. of hemorrhagic shock. This study investigates the effect of a novel, potent and selective inhibitor of iNOS activity (GW274150) on the circulatory failure and the organ injury and dysfunction associated with hemorrhagic shock in the anesthetized rat. Hemorrhage (sufficient to lower mean arterial blood pressure to 45 mmHg for 90 min) and subsequent resuscitation with shed blood resulted (within 4 h after resuscitation) in a delayed fall in blood pressure, renal and liver injury and dysfunction as well as the pancreatic injury. Pre-treatment of rats with GW274150 (5 mg/kg at 30 min prior to the onset of hemorrhage) attenuated the renal dysfunction as well as the liver and pancreatic injury caused by hemorrhage and resuscitation. Interestingly, GW274150 did not reduce the delayed fall in blood pressure associated with hemorrhagic shock. We propose that an enhanced formation of NO from iNOS contributes to the organ injury and dysfunction in hemorrhagic shock, and that highly selective inhibitors of iNOS activity, such as GW274150, may represent a novel therapeutic approach for the therapy of hemorrhagic shock.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:804285 CAPLUS
DN 138:314136
TI Beneficial effects of GW274150, a novel, potent and selective inhibitor of iNOS activity, in a rodent model of collagen-induced arthritis
AU Cuzzocrea, Salvatore; Chatterjee, Prabal K.; Mazzon, Emanuela; McDonald, Michelle C.; Dugo, Laura; Di Paola, Rosanna; Serraino, Ivana; Britti, Domenico; Caputi, Achille P.; Thiemermann, Christoph
CS School of Medicine, Institute of Pharmacology, University of Messina, Policlinico Universitario, Gazzi, Messina, 98100, Italy
SO European Journal of Pharmacology (2002), 453(1), 119-129
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
AB The aim of this study was to investigate the role of inducible nitric oxide synthase (iNOS) on the modulation of the inflammatory response in mice subjected to collagen-induced arthritis. Collagen-induced arthritis was induced in wild-type mice (iNOS-WT) treated with GW274150, a novel, potent and selective inhibitor of iNOS activity, and in mice lacking the gene for iNOS (iNOS knock-out', iNOS-KO), by an intradermal injection of 100 μl of emulsion containing 100 μg of bovine type II collagen and complete Freund's adjuvant at the base of the tail. After 21 days, a second injection of type II collagen in complete Freund's adjuvant was administered. iNOS-WT mice developed erosive hind paw arthritis when immunized with type II collagen in complete Freund's adjuvant. Over a 35-day period, macroscopic clin. evidence of collagen-induced arthritis first appeared as periarticular erythema and edema in the hind paws. By day 28, the incidence of collagen-induced arthritis was 100% in type II collagen-challenged iNOS-WT mice and the severity of collagen-induced arthritis progressed with radiog. evaluation revealing resorption of bone. Histopathol. of collagen-induced arthritis mice demonstrated erosion of

the cartilage at the joint margins. iNOS-WT mice treated with GW274150 (5 mg/kg, i.p. daily) starting at the onset of arthritis (day 23), and iNOS-KO mice showed a delay of the development of the clin. signs at days 24-35 and an improvement of the histol. status in the knee and paw. Immunohistochem. anal. for nitrotyrosine and for poly(ADP-ribose) polymerase revealed pos. staining in inflamed joints from type II collagen-treated iNOS-WT mice. The degree of staining for nitrotyrosine and poly(ADP-ribose) polymerase were markedly reduced in tissue sections obtained from type II collagen-treated iNOS-WT mice, who had received GW274150 and from iNOS-KO mice. Furthermore, radiog. signs of protection against bone resorption were present in the joints of iNOS-WT mice treated with GW274150 as well as in the joint from iNOS-KO mice. This study provides the first evidence that GW274150, a novel, potent and selective inhibitor of iNOS activity, attenuates the degree of chronic inflammation and tissue damage associated with collagen-induced arthritis in mice. Furthermore, these results suggest that the induction of iNOS and NO production are essential for the up-regulation of the inflammatory response during exptl. collagen-induced arthritis.

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:597331 CAPLUS
DN 136:288829
TI GW274150 is a potent, long-acting, highly-selective inhibitor of inducible nitric oxide synthase (NOS-2) with therapeutic potential in post-operative ileus
AU Alderton, W.; Angell, A.; Clayton, N.; Craig, C.; Dawson, J.; Frend, A.; McGill, J.; Mangel, A.; Moncada, S.; Rees, D.; Russell, L.; Schwartz, S.; Waslidge, N.; Knowles, R.
CS Glaxo Wellcome R and D, Stevenage, SG1 2NY, UK
SO Portland Press Proceedings (2000), 16(Biology of Nitric Oxide, Part 7), 22 CODEN: POPPEF; ISSN: 0966-4068
PB Portland Press Ltd.
DT Journal
LA English
AB GW274150 [(S)-2-amino-7-acetamidino-5-thioheptanoic acid] is a novel α-amino acid that potently inhibited human inducible nitric oxide synthase (iNOS) with selectivity vs. human eNOS and nNOS. In studies with purified NOS isoforms, GW274150 was a time-dependent, arginine-site inhibitor of iNOS and a rapidly-reversible inhibitor of eNOS. This novel compound had a long pharmacokinetic half-life and high oral bioavailability in several species. The selectivity of GW274150 against the constitutive NOS isoforms was maintained in vivo, the compound producing no significant effect on conscious mouse blood pressure dosed at 100 mg/kg and on rat brain plus nitrite levels at 50 mg/kg. Post-operative ileus is one potential therapeutic application for GW274150. In a rat model of post-operative ileus, GW274150 was maximally effective at 1-5 mg/kg, yielding a 67% reversal of delayed GI transit. The compound was also effective in a rat model of acute inflammatory pain (adjuvant).
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:209102 CAPLUS
DN 133:12344
TI Inhibition of inducible nitric oxide synthase by acetamidine derivatives of hetero-substituted lysine and homolysine
AU Young, Robert J.; Beams, Richard M.; Carter, Keith; Clark, Helen A. R.; Coe, Diane M.; Chambers, C. Lynn; Davies, P. Ifeyinwa; Dawson, John; Drysdale, Martin J.; Franzman, Karl W.; French, Colin; Hodgson, Simon T.; Hodson, Harold F.; Kleanthous, Savvas; Rider, Peter; Sanders, Daniela; Sawyer, David A.; Scott, Keith J.; Shearer, Barry G.; Stocker, Richard; Smith, Steven; Tackley, Miriam C.; Knowles, Richard G.
CS Glaxo Wellcome Research and Development, Stevenage, SG1 2NY, UK

SO Bioorganic & Medicinal Chemistry Letters (2000), 10(6), 597-600
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
AB The synthesis and in vitro evaluation of the acetamidine derivs. of hetero-substituted lysine and homolysine analogs have identified potent inhibitors of human nitric oxide synthase enzymes, including examples with marked selectivity for the inducible isoform.
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:753054 CAPLUS
DN 131:346497
TI Use of nitric oxide synthase inhibitors in the manufacture of a medicament for the prophylaxis or treatment of bacterial infection
IN Alderton, Wendy Karen; Knowles, Richard Graham; Ladel, Christoph Hubertus
PA Glaxo Group Limited, UK
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9959566	A1	19991125	WO 1999-EP3265	19990512
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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PRAI GB 1998-10299	A	19980515		
WO 1999-EP3265	W	19990512		

OS MARPAT 131:346497
AB Inducible nitric oxide synthase inhibitors are used for the manufacture of a medicament for the prophylaxis or treatment of a bacterial infection, where the inhibitor of inducible nitric oxide synthase is e.g. HN:C(R1)NHR2 [R1 = C1-6 straight or branched chain alkyl; Q = QC(NH2)CO2H (Q = alkylene, alkenylene, etc.), ring-substituted benzyl] or a pharmaceutically acceptable salt, ester, or amide thereof.
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:490618 CAPLUS
DN 129:122862
TI Preparation of S-[2-(1-iminoethylamino)ethyl]homocysteine as nitric oxide synthase inhibitor
IN Beams, Richard Mansfield; Drysdale, Martin James; Franzman, Karl Witold; Frend, Anthony Joseph; Hodson, Harold Francis; Knowles, Richard Graham; Rees, Daryl David; Sawyer, David Alan
PA Glaxo Group Ltd., UK; Beams, Richard Mansfield; Drysdale, Martin James; Franzman, Karl Witold; Frend, Anthony Joseph; Hodson, Harold Francis; Knowles, Richard Graham; Rees, Daryl David; Sawyer, David Alan
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9830537	A1	19980716	WO 1998-EP96	19980109
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
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	SK 283201	B6	20030304	SK 1999-933	19980109
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	W: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW				
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	US 1999-341220	A1	19990824		

OS MARPAT 129:122862

AB HN:CMeNHCH2CH2SCH2CH2CH(NH2)CO2H (I) was prepared for use as a selective inhibitor of nitric oxide synthase (NOS). Thus, (S)-I was prepared by treatment of L-homocystine with Na in liquid NH3 and then N-benzyloxycarbonylethanolamine tosylate, cleavage of the benzyloxycarbonyl protecting group with HBr in AcOH, and reaction with Et acetimidate hydrochloride. (S)-I was assayed for inhibition of inducible and endothelial NOS (IC50 = 0.73 and 43 μM, resp.).

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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---Logging off of STN---

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Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	59.41	114.30

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-10.95	-10.95

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